either when they are kept in darkness in the laboratory or when examined in the condition in which they are found in the total darkness of their natural habitat. It is difficult to see how these cells could have appeared in the peritoneum by a migration process, and they certainly have not appeared by an infective process such as Dr. Medawar has described, for they are completely isolated cells. Dr. Goodrich's idea of a "reservoir" of chromatoblasts in the fish dermis may also apply to the perineural and coelomic pigmentation. It is also interesting to note that the appearance of melanophores in these blind fish kept in the light is not mediated optically in any way. The fish lack a lens and retina, and many specimens also lack an optic nerve.

REFERENCE.

1. RASQUIN, P. Progressive pigmentary regression in fishes associated with cave environments. *Zoologica*, 32(4):35-42, 1947.

The Origin of Modifying Genes that Influence the Normal and Atypical Growth of Pigment Cells in Fishes.*

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In natural populations of platyfishes and swordtails no melanotic tumors were discovered in more than 10,000 specimens. Under laboratory conditions, when a spotted member of one natural population is mated to that of another, tumors develop in their spotted hybrids.

When a platyfish, *Platypoecilus maculatus*, with the spotted (macromelanophore) pattern is mated with the related genus, the swordtail, *Xiphophorus hellerii* (with which it is sympatric in southern Mexican rivers), the spotted intergeneric hybrids develop melanomas. When the spotted *Platypoecilus maculatus* is mated with another platyfish species (whose natural habitat is a thousand miles to the north), *Platypoecilus couchianus*, from the Rio Grande, the spotted interspecific hybrids also develop melanomas. When a spotted *Platypoecilus maculatus* is mated to a member of a nearby species, *Platypoecilus variatus*, from the Rio Panuco, the degree of atypical pigment cell growth in the spotted hybrids is less severe.

When a spotted *Platypoecilus maculatus* from the Rio Coatzacoalcos is mated to a member of the *same* species, *Platypoecilus maculatus*, from the Rio Jamapa, the *intraspecific* spotted hybrids show a definite melanosis very much like those between *P. maculatus* and *P. variatus*. The significant point is that the parents in each type of mating (intergeneric, interspecific, intraspecific) represent *different genetic populations*. Melanomas or melanoses develop in hybrids in response to a genic imbalance between the genes for macromelanophores, five of which have been identified, and their growth regulators, specific macromelanophore modifying genes, two of which are known.

These results may be explained by the same genetic principles that apply in explaining the origin of organic diversity and the mechanisms of the origin of species. When a population of individuals belonging to a single species is separated into two aggregations, as by a geological accident or by other forces, and that separation is maintained rigidly so that interbreeding between them is prevented, the two populations will, in time, become genetically distinct. The isolated populations become different owing to the ever-occurring, mutational changes. The genic changes that appear in members of the first population are not likely to be the same as the mutations that occur in the second. In time the random mutations accumulate in each of the two populations and eventually they make the two groups recognizably different. The rapidity of the genic changes depends on the size of the breeding population, the environment, as well as upon time. As genetically interpreted, the piling up of these small changes, each meeting the challenge of natural selection successfully, constitutes the very beginning of the speciation process.

There are six known natural populations of the platyfish, *Platypoecilus maculatus*, in the Atlantic coast rivers of Mexico, Guatemala and British Honduras. Each of these six populations differs genetically in the frequencies of five macromelanophore pattern genes. Although these populations have been isolated geographically for more than 300,000 years, their morphological differences are insufficient to indicate an evolutionary change at the subspecific level. They are, however, genetically distinct and these genetic differences can account for the genetic imbalance in the hybrid offspring of members representing different river populations.

Far back in geological time all platyfishes were probably like most fishes of their kind that are uniformly colored, unmarked by macromelanophores. In time the first "spotted" mutant appeared in a platyfish population, and transformed some previously existing cells into *macromelanophores*. The nature of the mutation process is not yet

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clear, but it is believed that mutations act like enzymes and affect the body chemically. Like most mutations, the macromelanophore mutation was probably harmful and most likely lethal, because most mutations upset an organism's established genetic balance and this, in turn, upsets the biochemical processes in the developing organism.

Prior to the spotted mutation's successful establishment in the platyfish population, mutations which were to serve, in part, as modifiers and controllers of the activity of macromelanophores must have accumulated first, and then neutralized the lethal effects of the spotted mutants when they reoccurred. The platyfish had to be made ready genetically for the coming of the spotted mutations by first accumulating macromelanophore controlling genes. When ready, the platyfish "accepted" macromelanophores without danger to themselves. However, when a genetically balanced spotted platyfish from the Rio Coatzacoalcos is mated with another normal member from the Rio Jamapa, the new recombination of genetic modifiers of macromelanophore growth is not in balance in the spotted hybrids, and these large pigment cells grow atypically. The hereditary effects of macromelanophores can be demonstrated genetically, as well as the effects of gene modifiers which influence macromelanophore growth patterns. The macromelanophores are genetically labile cells subject to normal or typical growth by a series of modifying genes.

References.

Dobzhansky, Th. Genetics and origin of species. Columbia Univ. Press, 1941.

Gordon, Myron. Biology of Melanomas. *N. Y. Acad. Sci., Spec. Pub.*, 4:216-268, 1948.

———— *Animal Kingdom*, 52:118, 1949.

———— *Endeavour*, 9:26-34, 1950.

Discussion by W. E. Heston, National Cancer Institute, Bethesda, Md.

The observations of Dr. Gordon are of especial interest to one studying the inheritance of cancer in mice because of the parallels to his observations that have occurred with mice. In general one can expect a greater variety of tumors to occur in hybrids between two inbred strains of mice than occur in either inbred strain. Little reported that in the F_1 hybrids resulting from crossing *Mus bactrianus* with strain C_{57} black *(Mus musculus)* the incidence of non-epithelial tumors was 39.7%, whereas that for the C_{57} black mice was 13.2% and no such tumors were recorded for the *Mus bactrianus* stock. In the history our experimental colony, 10 mice with tumors of the Harderian gland have occurred, and all of these have been hybrids from a specific cross (strain $C_3H \times$ strain C_{57} black). While this is a rare tumor, its occurrence in these specific hybrids and not in either parent strain or any of the other strains of the colony is remarkable.

The variation in degree of atypical pigment cell growth from melanosis to true melanomas effected by the genotypes of the different types of hybrid platyfish might also be compared with the variation in degree of expression of different genotypes affecting tumor formation in the mouse. This is particularly well illustrated with induced lung tumors. One observes from few to many nodules per animal, depending upon its genotype. Dr. Gordon's observation of melanosis in certain types of hybrids compared with true melanomas in other types suggests that with the carcinogen 5, 9, 10—trimethyl—1, 2—benzanthracene that produces pigmented foci in the skin of mice of certain strains, one might be able to produce true melanomas in other strains or hybrid types with a more suitable genotype.

Third Session: Physiological.

Introduction.

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The papers in this group hold a place of basic interest. We have had the abnormal pigment cell and its destructive effect on the organism discussed from the pragmatic empirical medical approach. We have had the genetic control of the cell within the organism discussed. Now we turn to the normal cell and its biologic behavior, considered as acting as an individual entity functioning cooperatively with other cells within the organism, its growth differentiation and regeneration, and the part it plays as a normal component of the organism.

It is this behavior that in the end will serve as a criterion for all theories of its structure or of the physical and chemical mechanisms posited as inherent in the cell. This is how it behaves as a biological entity and it is this behavior that we are seeking to understand by the biochemical or biophysical approach. Its abnormal behavior, as for instance in cancer, will eventually also be comprehended as a part of this story.